UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/091,578	10/06/1998	EDWIN L. MADISON	19191.0002	5096

30542 7590 02/09/2005

FOLEY & LARDNER
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
SCHWADRON, RONALD B	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/091,578	MADISON ET AL.	
	Examiner	Art Unit	
	Ron Schwadron, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 68-91 is/are pending in the application.

4a) Of the above claim(s) 73,76,79,83 and 85 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 68-72,74,75,77,78,80-82,84,86-91 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/15/2004 has been entered.

2. Claims 68-72,74,75,77,78,80-82,84,86-91 are under consideration.

3. The amendment to the specification filed 12/19/2003, line 4 recites "US 99/20577" wherein it should recite US 96/20577.

4. The previously pending rejections of claims 68-72,74,75,77,78,80-82,84,86-89 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons elaborated in the previous Office Action is withdrawn in view of the amended claims.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 68-72,74,75,77,78,80-82,84,86-91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of "suitable for administration in vivo" in claim 68. Regarding the specification, page 13, the cited passage refers to a definition of the therapeutic entity, not the therapeutic agent recited in the claims. Furthermore, said passage does not recite the term "suitable

for administration". The specification does not recite the term "suitable for administration" or define the parameters which are encompassed by "suitable for administration in vivo". There is no support in the specification as originally filed for the scope of the claimed invention (eg. the claims constitute new matter for the reasons stated above).

7. The instant claims as amended do not encompass a surface loop attached to the end of a molecule (eg. not inserted into a protein).

8. The rejection of claims 68-72,74,75,77,78,80-82,84,86-89 under 35 U.S.C. 103(a) as being unpatentable over Quertermous et al. (US Patent 5,811,265) in view of Rodwell (US Patent 5,196,510) and Barbas et al.(1993) for the reasons elaborated in the previous Office Action is withdrawn in view of the amended claims.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 68,71,81,82,84,86,91 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolfson et al. as evidenced by Lezdey et al. (US Patent 6,124,257). Applicants arguments have been considered and deemed not persuasive.

Wolfson et al. teach that the elastase protease binding surface loop EAIPMSIPPE can be substituted into the cytokine interleukin-1β (see abstract and page 316, second column, *Discussion*, continued on next page). It is an inherent property of elastase that it is a "modulator of angiogenesis" (see Lezdey et al., column 1, paragraph 6). Wolfson et al. disclose that said loop maintains a specific binding characteristic (eg. it binds the appropriate protease (a protein enzyme), see abstract). Wolfson et al. indicate that the interleukin-1β would be expected to retain its binding specificity (see abstract, last sentence) and that the overall structure of the mutant is indistinguishable

from wild type (see abstract), wherein said mutant protein has therefore retained a therapeutic property. The mutant protein is recombinantly prepared. Wolfson et al. disclose that the exogenous loop replaces a removed surface loop (see page 313, second column, last paragraph, continued on page 314). Wolfson et al. disclose that "this hybrid protein also demonstrates the feasibility of using interleukin-1β as a delivery system for useful therapeutic agents". Thus, said molecule is "suitable for administration in vivo" and is an entity having "a therapeutic property".

Regarding applicants comments, Wolfson et al. disclose that "this hybrid protein also demonstrates the feasibility of using interleukin-1β as a delivery system for useful therapeutic agents". Thus, said molecule is "suitable for administration in vivo" and is an entity having "a therapeutic property". Regarding applicants comments about Grutter et al. and Labriola-Tomkins et al., the Labriola-Tompkins et al. reference actually teaches that binding to type II IL-1R is unaffected by the various mutations that were made in interleukin-1β (see abstract). Thus the molecule taught by Wolfson et al. would have a therapeutic property (binding to type II IL-1R). In addition, there is no evidence of record that the particular molecule taught by Wolfson et al. would have impaired interleukin-1β effector function wherein said effector function would constitute "a therapeutic property". Furthermore, both Grutter et al. and Labriola-Tomkins et al. refer to particular amino acid substitutions wherein none of the particular substitutions reported in said publications are found in the molecule taught by Wolfson et al.

11. Claims 68-72,74,75,77,78,80-82,84,86,90,91 are rejected under 35 U.S.C. 102(b) as being anticipated by Maeda et al. as evidenced by Balint, Jr. (US Patent 5,075,423),Uhlen et al. and Barbas et al. (1993). Applicants arguments have been considered and deemed not persuasive.

Maeda et al. teach insertion of RGDS peptide into truncated recombinant Protein A (see abstract). Said molecule constitutes a protein as per the definition of said word on page 12 of the specification. Protein A is recognized in the art as a therapeutic agent having a therapeutic property which has been used in vivo(for example see Balint, Jr., column 1, paragraphs 3 and 5). Furthermore, even ex vivo use of protein A requires a form of protein A "suitable for in vivo administration" because a portion of the protein A would be

leached in vivo (see column 1, paragraph 5). RGDS binds integrins (see page 15165, first column, last sentence). The RGD motif inherently binds αIIbβ3 integrin (see Barbas et al. page 10003, column 2. first incomplete paragraph) which is inherently found on the surface of platelets (see Barbas et al. page 10003, column 2. first incomplete paragraph) wherein platelets form blood clots. Maeda et al. disclose that the grafted RGDS forms a surface loop in the truncated protein A molecule (see page 15167, second column, last paragraph, continued on next page). Regarding claim 69, in view of the fact that the RGD motif is found in molecules that do not have cell adhesion activity (see page 15167, first column, last paragraph), the grafted peptide has been optimized to increase its natural affinity for target. The grafted RGDS peptide is functionally active and retains its binding specificity (see abstract) and the mutant truncated protein A retains a therapeutic property (eg. ability to bind IgG, see abstract). Protein A binds IgG wherein said molecule can occur on the surface of B cells. The RGDS peptide is inserted into the middle of the protein A molecule (see Figure 1 of Maeda et al.) wherein Uhlen et al. (Figure 6 and page 1699) indicate that the middle of the protein A molecule would inherently encompass a region "between two regions of secondary structure" because the protein A molecule inherently consists of 5 IgG binding regions (regions of secondary structure) wherein the middle of the protein A molecule is in the middle of said five separate binding regions.

Regarding applicants comments, the RGDS peptide is inserted into the middle of the protein A molecule (see Figure 1 of Maeda et al.) wherein Uhlen et al. (Figure 6 and page 1699) indicate that the middle of the protein A molecule would inherently encompass a region "between two regions of secondary structure" because the protein A molecule inherently consists of 5 IgG binding regions (regions of secondary structure) wherein the middle of the protein A molecule is in the middle of said five separate binding regions. Regarding applicants comments about Balint et al., the MPEP section 2121 discloses:

PRIOR ART IS PRESUMED TO BE OPERABLE/ ENABLING
When the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). See also

MPEP § 716.07.

There is no evidence of record that the Balint et al. reference lacks enablement regarding the use of Protein A as a therapeutic agent having a therapeutic property. Protein A is recognized in the art as a therapeutic agent having a therapeutic property which has been used in vivo(for example see Balint, Jr., column 1, paragraphs 3 and 5). Furthermore, even ex vivo use of protein A requires a form of protein A "suitable for in vivo administration" because a portion of the protein A would be leached in vivo (see column 1, paragraph 5).

12. Claims 68-72,74,75,77,78,80-82,84,86-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quertermous et al. (US Patent 5,811,265) in view of Wolfson et al., Maeda et al., Rodwell (US Patent 5,196,510) and Barbas et al.(1993).

Quertermous et al. teach tPA/antibody fragment recombinant conjugates (see abstract, column 2, second paragraph and column 7, fourth paragraph). tPa has been used therapeutically in vivo in humans (see column 4 of Quertermous et al.). Quertermous et al. do not teach that the conjugate contains the surface loop HCDR3 from Fab-9 inserted into the tPA molecule as per recited in claim 68. Wolfson et al. teach that the elastase protease binding surface loop EAIPMSIPPE can be substituted into the cytokine interleukin-1β (see abstract and page 316, second column, *Discussion*, continued on next page). Maeda et al. teach insertion of RGDS peptide into truncated recombinant Protein A (see abstract). Both Wolfson et al. and Maeda et al. teach that the binding moiety is inserted into the target molecule in a manner encompassed by that recited in the claims (Maeda et al. teach insertion of RGDS peptide into the middle of truncated recombinant Protein A whilst Wolfson et al. teach that the elastase protease binding surface loop EAIPMSIPPE can be substituted into the cytokine interleukin-1β). Barbas et al. disclose Fab-9 monoclonal antibody wherein an optimized RGD peptide was inserted into HCDR3 (heavy chain CDR3) of said Fab (see pages 10004 and 10005). Barbas et al. teach that the inserted amino acid sequence mediates binding to the adhesion/adhesive protein integrin αIIbβ3 wherein said integrins are cell surface proteins found on platelets(see page 10006, first column) and wherein platelets are found in blood clots. Rodwell et al. teach that CDR3 peptides derived from an antibody with a particular specificity can be optimized for binding (see column 24-25) and used in

a conjugate to target the conjugate to a desired target (see columns 18-21). The HCDR3 of Barbas et al. has been optimized to increase its natural binding affinity (see column 2, page 10004). The integrin bound by the conjugate is a platelet cell surface protein. The integrin binds to the RGD motif found in Fab-9 CDR3 (see abstract). tPA is a thrombolytic agent (see column 2, second paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Quertermous et al. teach tPA/antibody fragment recombinant conjugates whilst Wolfson et al. and Maeda et al. teach that the binding moiety is inserted into the target molecule in a manner encompassed by that recited in the claims and Barbas et al. disclose Fab-9 monoclonal antibody wherein an optimized RGD peptide was inserted into HCDR3 (heavy chain CDR3) of said Fab and that the inserted amino acid sequence mediates binding to the adhesion/adhesive protein integrin αIIbβ3 and Rodwell et al. teach that CDR3 peptides derived from an antibody with a particular specificity can be used in a conjugate to target the conjugate to a desired target (see columns 18-21). One of ordinary skill in the art would have been motivated to do the aforementioned because Barbas et al. teaches that the RGD motif can be used to bind a biomolecule to an integrin and the role of integrins in a variety of disease states whilst Rodwell et al. teach that CDR3 binding peptides derived from an antibody with a particular specificity can be used in a conjugate to target the conjugate to a desired target. In addition, Quertermous et al. teach tPA/antibody fragment recombinant conjugates and the potential uses of such conjugates (see abstract). Furthermore, Maeda et al. disclose that the potential therapeutic uses of proteins that contain inserted integrin binding moieties (see page 15168, last paragraph)

Regarding the Madison et al. declaration, the statements in paragraph 8 of said declaration regarding the Smith et al. reference are contradicted by the actual teachings of the Smith et al. reference. Said reference states on page 32793, second column: ***We conclude that the synthetic peptide derived from the CDR3 of Fab-9 emulates the activity of the whole antibody and like Fab-9, maintains specificity for αvβ3 over the related integrin αvβ5.***

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached on Monday to Thursday from 7:30am to 6:00pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at 571 272 0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP ~~1800~~ 1600